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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

DIAGNOSTIC AND PROGNOSTIC IMPORTANCE OF SOME BIOCHEMICAL MARKERS DURING NECROTIZING ENTEROCOLITIS IN NEWBORNS

Speciality: 3220.01 – Pediatrics

Field of science: Medicine

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GENERAL DESCRIPTION OF THE WORK

Relevance of the theme. One of the actual problems of neonatology effected directly to illness and death indicators in infants is necrotizing enterocolitis (NEC) [1, 2].

NEC is non-specific inflammatory disease in newborns, a disease caused by infectious agents in the background of lack of local defense mechanisms and/or is a disease with generalization of inflammatory reactions as a result of hypoxic-ischemic damage of the intestinal mucosa [3, 4, 5].

According to D.Kloyerti (2002), NEC is an acute necrotic intestinal syndrome with uncertain etiology[6]. Although certain successes are acquired in this field in the modern period, NEC is still considered one of the diseases causing to child death in the first months of the life. Therefore, one of the main problems is to ensure early diagnosis and adequate treatment at the time of this pathology. The cases of NEC is encountered in 0,3-2,4% cases 1000 children.

These indicators are higher among children who have premature birth and intrauterine growth retardation and hesitate between 28-

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54% [7, 8].

The number of cases of NEC been increasing in regard to the increase of living indicators of children with premature birth and extremely low birth weight during the last 20 years [9, 10]. Etiology of NEC is multifactorial. Its main component is ischemia in prenatal period, abnormal colonization of intestine of newborns and inadequate feeding of child in postnatal period.

Despite of the multiple scientific investigations dedicated to NEC, its pathogenesis, early diagnosis, treatment strategies, prognostic criterions, impact of different diseases to the course of NEC, etc. isare not entirely learned [11].

Recent years, wide discussions are conducted about use of biochemical markers in the direction of assessment and forecasting of activity of inflammatory processes at the time of different pathologies in newborns. With help of biochemical markers, the significance of the course of disease is determined and accurate treatment method is chosen accordingly.

However, learning of biochemical markers at the time of NEC, principally, bears experimental character and their diagnostic importance in pathogenesis of disease is not learned fully. Thus, application of diagnostic methods assessed pathogenetically creates an opportunity for development of prognostically and scientifically sub-

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stantiated new and modern treatment tactics of necrotizing enterocolitis. In this regard, scientific work submitted by us is dedicated to just that problem.

Object and subject of research. 110 newborn children with necrotizing enterocolitis, regardless of gestational age and weight, were included in the research. These children were divided into groups according to the course stages of NEC. The control group formed 30 practically healthy newborn children.

The purpose of the study. Diagnostics of necrotizing enterocolitis in newborns is to learn the importance of some biochemical markers in its clinics and forecasting.

Research objectives:

1. Observation of ante-and postnatal risk factors in development of necrotizing enterocolitis in newborns.
2. Assessment of clinic and diagnostic role of fecal calprotectin which is non-invasive marker of inflammatory process in intestine at the time of necrotizing enterocolitis.
3. Assessment of matrix metalloproteinases, antimicrobial peptide-cathelicidin blood and concentration of blood plasma protein transferrin during necrotizing enterocolitis in newborns.
4. Learning of clinic and diagnostic importance of biochemical markers – matrix metalloproteinases and their tissue inhibitors depending on course and stages of disease during necrotizing enterocolitis in newborns.
5. Investigation of correlation relationship among molecular and biochemical markers and assessment of prognostic importance of these indicators.

Methods of research. Analysis of biochemical, serological examinations, clinical and laboratory information was conducted in clinical, biochemical and immunological laboratories of Scientific-Research Pediatric Institute named after K.Y.Farajova in research work. As children enter the hospital, general examination of blood, urine and feces, bacteriological examination of blood, determination of intrauterine infections in blood, biochemical examination of blood and determination of MMP-17,-9,-2 out of biochemical markers, cathelicidin, transferrin and fecal calprotectin was conducted in chil-

dren with NEC. These examinations were continued in dynamics too.

The main provisions of the defense:

– The change was observed in indicators of biochemical markers depending on stages of disease during necrotizing enterocolitis in newborns.

– Significant change of the level of biochemical markers at the time of necrotizing enterocolitis was directly proportional to the course of necrotizing enterocolitis in newborns. Moreover, direct connection was recorded between stages of disease and level of biochemical markers.

– The change of concentration of matrix metalloproteinases at the time of necrotizing enterocolitis in newborns indicates complication of necrotic damage in intestine, manifestation of skeptical process and thus, high probability of non-satisfactory result.

Scientific innovation of research.

- Ante-postnatal risk factors causing to development of necrotizing enterocolitis in newborns and their mothers were studied and correlation relationships among risk factors were determined at this time.

- Biochemical markers (matrix metalloproteinases - MMP-2, MMP-9, MMP-17, cathelicidin, transferrin and fecal calprotectin) depending on severity and stages of necrotizing enterocolitis in newborns were studied complexly.

- The level of fecal calprotectin which is inflammatory marker of gastrointestinal system at the time of necrotizing enterocolitis was investigated and the use of this marker as non-invasive marker in diagnosis of necrotizing enterocolitis was substantiated. It was determined that-, a change of concentration of fecal calprotectin is related to severity of necrotizing enterocolitis in newborns, and it determines the activity of acute inflammation in intestine and degree of pathological process.

- The level of matrix metalloproteinases which is the family of extracellular endopeptide was examined at the time of necrotizing enterocolitis and it was determined that, increase of concentration of blood plasma of matrix metalloproteinases-17, matrix metalloproteinases-9 and matrix metalloproteinases-2 shows the complica-

tion of inflammatory process.

- Correlation relationships giving an opportunity to assess the clinical and diagnostic importance of biochemical markers (matrix metalloproteinases, cathelicidin, transferrin and fecal calprotectin) including in research were determined with degree of severity of necrotizing enterocolitis in newborns.
- Prognostic importance of biochemical markers, the impact power on the course of disease, as well as mutual dependence among markers were determined at the time of necrotizing enterocolitis on the basis of examinations conducted.

Theoretical and practical importance of research.

The use of biochemical markers reflecting the activity of inflammatory process in intestines at the time of necrotizing enterocolitis in newborns bears practical importance in early diagnosis.

The analysis of indicators of biochemical markers before and after treatment confirms a diagnostic importance of these markers, and it creates a condition for their use in clinical practice as a predictor of intestinal damages and septic complications.

Approbation. The main provisions of dissertation were reflected in lectures and discussions: VIII Congress of Pediatricians of the CIS countries, Kyrgyzstan (2016), conference dedicated to the 100th anniversary of academician V.Akhundov (2016), conference dedicated to the 90th anniversary of the birth of the honored scientist, prof.A.A.Aliyev (2016), scientific-practical conference on the subject of "Təbabətin actual problemləri" dedicated to the 25th anniversary of the State Independence of Azerbaijan (2017), conference on the subject of "Uşaqlıq dövrünün nevroloji xəstəlikləri" (2018); conference on the subject of "Səhiyyədə müasir nailiyyətlər" dedicated to the 95th anniversary of the birth of academician Z.Aliyeva (2018), conference dedicated to the 95th anniversary of honored scientist, prof. T.A.Taghizada (2018), international scientific practical conference dedicated to actual problems of "Tibbin görən gözü" radiation diagnostics (2019), conference dedicated to the 90th anniversary of the honored scientist, prof.D.V.Hajiyev (2019), XVIII International Eurasian Congress of Surgery and. Hepatogastroenterology (2019), 17.UNPSTR- Eurasian Congress (2019), Congress of Pediatrics and

Pediatric Surgery of Tajikistan (2019), international scientific-practical congress on the subject of "Təbabətin aktual problemləri-2020" dedicated to the 90th anniversary of Azerbaijan Medical University (2020), IX Congress of Pediatricians of Kazakhstan (2021).

The first discussion of dissertation work was conducted on 27 June 2019 in the joint meeting of associates of the departments of "Child diseases" of Azerbaijan Medical University and Scientific-Research Pediatric Institute named after K.Y.Farajova (protocol №2). Dissertation work for defense was discussed in the meeting No 18 2021 October 08 of ED 2.27 Dissertation Board acting under AMU.

Application of the research. The results obtained were applied in the work of the departments of anesthesiology, intensive care unit and intensive therapy, pathology of premature infants, neonatal pathology and surgery of early aged children of Scientific-Research Pediatric Institute named after K.Y.Farajova.

Publications. 24 scientific works on dissertation work, in addition to 10 articles and 14 theses were published.

Name of the organization of realization the dissertation. The work presented was conducted in the departments of anesthesiology, intensive care unit and intensive therapy, pathology of premature infants, neonatal pathology and surgery of early aged children of Scientific-Research Pediatric Institute named after K.Y.Farajova.

Structure and volume of dissertation. Dissertation was written in Azerbaijani language, it was submitted with 148 pages (192.400 symbols), consists of 34 tables, 12 photos: introduction (9.300 symbols), literature review (60.000 symbols), chapter of material and methods (12.600 symbols), 3 chapters of personal research (16.800+36.900+27.000 symbol), summary, results, practical recommendations (29.800 symbol), list of literature consisting of 153 sources, abbreviations and conventional signs.

MATERIAL AND METHODS OF RESEARCH

The work presented was conducted in the departments of anesthesiology, intensive care unit and intensive therapy, pathology of premature infants, neonatal pathology and surgery of early aged children of Scientific-Research Pediatric Institute named after K.Y.Farajova.

In order to carry out the tasks set, 110 ill newborns with NEK were examined. The children examined entered to Scientific-Research Pediatric Institute from maternity homes of Baku city and regions. These children were divided into the following groups for stages of course of NEC: I group – 49 patients which is I stage of NEC, II group – 48 patients which is II stage of NEC, III group –13 patients which is III stage of NEC. Practically health 30 newborns constituted the control group. They were examined in neonatology department of maternity home No 7.

Observations and examinations were conducted in dynamics and when patient entered clinic. Diagnosis was made based on clinical view, additional examination methods and instrumental examinations. Special examination cards indicating the detailed anamnesis, clinical diagnosis (dynamics and result of disease), results of examinations and treatments were prepared in the work for each child.

According to anamnestic information, the vast majority of children were born from mothers under the age of 30 (80 ± 3.8%). 62 infants from newborns were boys (56,4±4,7%) and 48 infants were girls (43,6±4,7%). When we look through groups, 30 of I group were boys (61,2%), 19 were girls (38,8%); 25 of II group were boys (52,1%), 23 were girls (47,9%). Number comparison of boys and girls in III group is almost the same – accordingly 7- 53,8% and 6- 46,2%.

Weights of children entered hospital were among 650-4200 gr, height was 33-54 cm, head circle was 27-37 cm, circle of thorax was 26-36 cm. So, on average the weight of I group children was 2190,0±99,4 gr; height was 46,3±1,1 cm; circle of thorax was 32,2±0,7 cm; circle of head was 33,1±0,6 cm; weight of II group

children was 2306,0±123,5 gr; height was 46,8±1,7 cm; circle of thorax was 30,8±0,9 cm; circle of head was 32,3±0,9 cm; weight of III group children was 2105,0±146,9 gr; height was 47,8±0,6 cm; circle of thorax was 31,0±1,5 cm; circle of head was 31,7±1,3 cm.

50 children were born with asphyxia; light asphyxia was followed in 28 newborns of them (56,0±7%), intermediate severe asphyxia was followed in 13 newborns (26,0±6,2%), severe asphyxia was followed in 9 newborns (18,0±5,4%). Severity of asphyxia was assessed in the 1st and 5th minutes with Apgar scale. When Apgar scale, was assessed, it was detected that, infants born with 9-10 scores were not observed in any group. 7-8 scores were in 7 children (33,3±10,3%), 4-6 scores in 11 children (52,4±10,9%), 1-3 scores in 3 children (14,3±7,6%) in I group at the time of assessment on Apgar scale in the 1st minute. The situation stabilized in the 5th minute and indicators of Apgar scale were determined 7-8 scores in 14 children (66,7±10,3%), 4-6 scores in 4 children (19,0±8,6%) and 1-3 scores in 3 children (14,3±7,6%).

When we look through II group, children born with 4-6 scores dominated (15 children - 78,9±9,4%). These indicators have improved in the 5th minute after rendering an appropriate assistance: satisfactory condition 7-8 scores were followed in 52,6±11,5%, 4-6 scores were followed in 47,4 ±11,5% cases.

Severe asphyxia (1-3 scores) was followed in the 1st and 5th minutes in 50±15,8% children in III group, exact difference was followed in I and II group at this time ($p<0,05$).

The majority of newborns entered were born prematurely (73 children). Children with gestation age of 38-40 and 35-37 weeks among I group newborns dominated (each of them -32,7±6,7%). Newborns with gestation age of 38-40 weeks in II group were much more (35,4±6,9%), the number of newborns with hesitation age of 35-37 weeks was much more in III group (38,5±13,5%). But, when looking at the overall percentage comparison, the percentage of premature births was higher.

General condition of examined children was assessed. The condition of 12 (10,9±3%) newborns was severe, condition of 88 (80,0±3,8%) newborns was very severe, condition of 10 (9,1±2,7%)

newborns was preagonal when they entered to hospital.

Analysis of all biochemical, serological examination, clinical and laboratory information was conducted in clinical, biochemical and immunological laboratories of Scientific-Research Pediatric Institute named after K.Y.Farajova. As children enter the hospital, general examination of blood, urine and feces in children, bacteriological examination of feces, determination of intrauterine infections in blood (cytomegalovirus, toxoplasmosis, herpes, rubella infection), biochemical examination of blood and determination of MMP-17,-9,-2, cathelicidin, transferrin and fecal calprotectin out of biochemical markers was conducted. These examinations were continued in dynamics.

Moreover, the children were examined by a neurologist, ophthalmologist, otolaryngologist, surgeon and other specialists. Distribution of NEC according to stages was specified after view of surgeon. Mothers of newborns were examined by a therapist, if necessary, by a gynecologist. Radiological examination of thorax, total X-ray examination of abdominal cavity and ultrasound examination of brain, heart and internal organs out of instrumental examination methods was conducted in children.

Ultrasound examination of brain in all children was conducted by means of Aloka-SSD 1400 Medelkom JLE 102 and "Microl mabes" firm «Ausonic» (Australia) diagnostic devices.

Nozzles with a frequency of 5 and 7.5 mgh, a special gel of the "Aquosonic" type for acoustic contact were used in examination with the "Ausonic" device.

Radiography of thorax and abdominal cavity, if instructed, contrast radiography (passage of GIT (gastrointestinal tract) with barium sulfate, irrigography) was conducted in all patients. X-ray examinations were conducted in stationary Shimatzu and portable Toshiba Portable X-ray Unit X-ray device.

Determination of biochemical markers was conducted in ElisysUnoHuman (Germany) full automatic analisator with reactives of CUSABIO BIOTECH firm by method of immunoenzyme.

The digital results conducted were analyzed statistically with medical statistic methods meeting modern requirements. Variation,

correlation, discriminant, dispersion and ROC-analysis methods were applied. Calculations were conducted in EXCEL-2010 electronic schedule and by means of SPSS-20 computer program.

RESULTS OF RESEARCH AND THEIR DISCUSSION

In order to determine ante-and intranasal risk factors of necrotizing enterocolitis in newborns by us, the anamnesis, course of pregnancy and retrospective assessment of birth were conducted in 110 mothers.

Birth of 63 (57,3±4,7%) women were treir first birth experience. The comparison of repeated births was 42,7±4,7%. The number of the first births in all three groups was higher- more. Thus, it was accordingly 55,1±7,1% in I group, 60,4±7,1% in II group and 53,8±13,8% in III group.

The complicated course of pregnancy was recorded in mothers from all groups.

The vomiting indicated a pathological course of pregnancy in the examined women. The vomiting was recorded in 93 (84,5±3,4%) mothers and preeclampsia was recorded in 35 (31,8±4,4%) mothers. The preeclampsia was followed mostly in I group mothers (38,8±7%).

The risk of miscarriage was observed totally in 19 mothers (17,3±3,6%). Anemia was observed at the time of pregnancy in 63,6±4,6% mothers (in I group - 63,3±6,9%, in II and III groups accordingly 70,8±6,6% and 38,5±13,5%). Intrauterine infections were observed in 23 mothers (20,9±3,9%) during pregnancy. Intrauterine infection was seen mostly in mothers of II and III group patients (accordingly 22,9±6,1% and 23,1±11,7%). In our examinations, 11,8±3,1% mothers had an acute respiratory viral infection (ARVI) in I and II trimester of pregnancy. ARVI was followed mostly in mothers of II and III groups (accordingly 16,7±5,4% and 23,1±11,7%).

Surgical birth was seen in 51,8±4,8% cases in the groups examined. The physiological birth happened in 53 mothers (48,2±4,8%). As it seems, surgical birth was conducted in almost,- half of mothers.

Particularly in I and III groups the number of mothers with surgical birth was higher (accordingly 55,1±7,1% and 53,8±13,8%).

In order to assess the relations among indicators, the correlation analysis was conducted. The results of correlation analysis were assessed in quantity by method of Spearman's rank and the following correlation relationships were determined correspondingly:

- Moderately stable correlation between vomiting of pregnant and anemia (ρ_s=0,454, p<0,001), moderate inverse correlation relationship between preeclampsia and gestation age (ρ_s=0,412, p=0,003)
- Weak inverse correlation relationship between extragenital pregnancy and gestation age (ρ_s=0,327, p=0,022) and risk of miscarriage (ρ_s=0,285, p=0,047).

Diagnosis and comparative clinic description of necrotizing enterocolitis in newborns. Clinic image of NEC in newborns is accompanied with signs of intoxication (unstable temperature, lethargy, bradycardia, apnea) and signs of damage of the gastrointestinal tract (vomiting with gall, accelerated excretion of feces, change of the composition of feces, presence of pathological impurities in feces - mucus and blood).

The development of disease was observed in 37 children (33,6±4,5%) up to 7 days, in 68 children (61,8±4,6%) during 8-28 days and in 5 children (4,5±2%) after 28 days.

The disease began acutely in all children. The signs of intoxication were followed in all children (100%). Vomiting with gall and change of character of feces was followed during I day of disease. 47 children (42,7±7,7%) were normal, but high temperature was followed in 63 children (57,3±4,7%). So, subfebrile temperature was recorded in 22 children (20±3,8%), febrile temperature in 20 children (18,2±3,7%), pyretic temperature in 3 patients (2,7±1,6%) and hyperpyretic temperature in 2 (1,8±1,3%) patients.

27 (24,5±4,1%) children out of patients examined were in natural feeding, 66 (60±4,7%) children in artificial feeding, 12 (10,9±3%) children in the mixed feeding and 5 (4,5±2%) children were not fed. The number of artificial fed children was more in all groups. This indicates that, artificial feeding is one of the main risk factors in the development of NEK.

Total X-ray examination of the abdomen, neurosonography, ultrasound examination of the abdomen and echocardiography examination was conducted in all patients who entered the hospital. Thickening of intestinal loops was followed in 42 (38,2±4,6%) children, meteorism in 69 (62,7±4,6%) children, pneumatosis in 34 (30,9±4,4%) children, free air in abdominal cavity in 12 (10,9±3%) children during total X-ray examination of abdominal cavity. When we look through groups, meteorism was observed much more during total X-ray examination in I group newborns (71,4±6,5%). Thickening of intestinal loops was observed in 21 (42,9±7,1%) patients, pneumatosis was observed in 8 (16,3±5,3%) patients. Free air was not observed. Meteorism was observed in 30 (62,5±7%) patients of II group, thickening of intestinal loops was observed in 15 (31,3±6,7%) patients and intestinal pneumatosis was observed in 22 (45,8±7,2%) patients. The condition was slightly different and more difficult in III group. So, free air was followed in abdominal cavity in all patients who entered the group, it is considered absolute indication for surgical operation. Meteorism was observed in 4 (30,8±12,8%) patients, thickening of intestinal loops was observed in 6 (46,2±13,8%) patients and signs of pneumatosis were followed in 4 (30,8±12,8%) patients.

Changes were observed in 64 children during echocardiography examination. At the time, functional oval hole was observed in 27 (24,5±4,1%) children, defect of the eardrum in 8 (7,3±2,5%) children, keeping the arterial flow open in 14 (12,7±3,2%) children, defect of the interventricular septum in 5 (4,5±2%) children, mitral regurgitation in 5 (4,5±2%) children and tricuspid regurgitation in 5 (4,5±2%) children.

Neurosonographic examination of brain was conducted in all children examined as they entered the hospital. At this time, cerebral hemorrhage out of the main indicators was observed in 29 (26,4±4,2%) patients, cerebrovascular disorders in 40 (36,4±4,6%) children, cerebral edema in 14 (12,7±3,2%) children, periventricular leukomalacia in 6 (5,5±2,2%) patients, brain cyst in 5 (4,5±2%) patients and brain abnormality in 2 (1,8±1,3%) patients.

Ultrasound examination of internal organs was conducted in all

patients. At the time, enlargement of the liver was followed in 55 (50±4,8%) patients, enlargement of the spleen in 10 (9,1±2,7%) patients and changes in kidneys was followed in 37 (33,6±4,5%) patients.

When we look through groups, changes by hepatobiliary system were followed mostly in I group - 55,1±7,1%, 32,7±6,7%. Changes by kidneys were followed mostly in III group (38,5±13,5%), this indicates that their condition is more severe.

Several other diseases were observed in newborns with NEC, these complicated much more the course of the main disease. Special cases emerged in prenatal period dominated among co-occurring diseases at the time of NEC. The frequency of occurrence of these diseases among groups was the same between I and II group. The diseases of the respiratory system were at the second place for its frequency of occurrence (29,1±4,3%). Diseases of the blood and diseases of hematopoietic organs were observed mostly in II group, statistical accuracy was followed in I and III groups at this time. The frequency of occurrence of diseases of the genitourinary system was the same in I and II group. So, this indicator was accordingly 4,1±2,8% and 4,2±2,9%. The isolated or mixed infections were followed in all patients. Hypoxic encephalopathy - 82,7% (91), intrauterine infection - 60,9% (67), pneumonia - 28,2% (31), jaundice - 27,3% (30) and sepsis - 18,2% (20) was followed in the vast majority of patients.

When we look through biochemical indicators (total protein, calcium, potassium, sodium, albumin) on groups, it was observed that, these indicators were lower than norm in comparison with control group. Hypoproteinemia was approximately in the same degree in every three groups, it did not differ statistically accurately. Sodium was close to normal in group I, but hyponatremia was noticeable in II and III group and was 138,2±0,7 and 138,3±2,1 ($p_1<0,05$). C-reactive protein was high in comparison with control group in all groups, it approves the generalization of inflammatory process in patients and severity of process. So, C-reactive protein increased 1,3 times ($p_1<0,05$) in II group and 2,1 times ($p_1<0,001$) in III group in comparison with I group.

Intrauterine infections were determined in blood in 80 patients

out of patients with NEC. At this time, toxoplasmosis was observed in 10 (12,7±3,7%) patients, herpes in 8 (10,5±3,5%) patients and rubella infection in 3 patients. Cytomegalovirus infection was followed in all patients examined.

The general examination of urine and feces was conducted in all patients. As the result of general stool examination, high amount of neutral fats was found in 12,2±4,7% of patients in I group. It was found in III group during the general examination of feces that 61,5±13,5% of patients had high amounts of mucus, and 61,5±13,5% of patients had more than 30 leukocytes in the visual field. In III group, unlike other groups, more patients had fewer neutral fats. In III group patients, more erythrocytes and yeasts were noted during the general examination of feces (accordingly 46.2±13.8% and 69.2±12.8%).

Biochemical markers were identified in 50 patients and a comparative assessment was performed before and after treatment. It was determined at this time that in comparison with control group, MMP-2 increased 6,9 times in I group, 8,3 times in II group, 10,7 times in III group (accordingly 309,4±15,4; 374,1±23,4; 480,8±87,8). When MMP-2 compared with other groups in III group, accurate results were obtained with I and II groups. Similarly, MMP-9 increased 3 times in I group, 3,4 times in II group and 4,5 times in III group and was 544,1±25,4. MMP-9 differed significantly from the control group in I and II groups, as well as in III group, an accurate result was obtained with I and II groups.

The concentration of MMP-17 slightly differed from other MMPs. So, in comparison with the control group, MMP-17 increased at the same degree -2,5 times in I and II groups and 3,6 times in III group and accurately differed from other groups ($p_1<0,01$; $p_2<0,01$).

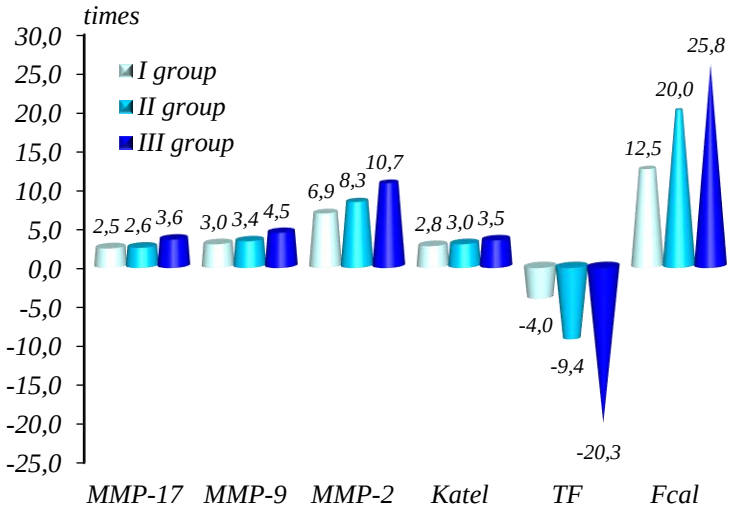
When we look at the level of cathelicidin in the blood serum, we see a significant increase in all groups compared to the control group. So, cathelicidin forms 40,3±1,0 in I group, 43,8±1,5 in II group and 50,9±2,4 ng/ml in III group. Accordingly, cathelicidin increased 2,8 in I group; 3 in II group; and 3,5 times in III group compared to the control group ($p<0,001$).

The level of fecal calprotectin was 0,317±0,110 in I group and

increased 12,5 times compared to the control group ($p<0,001$). The level of FC was 580,5±25,0 and 746,9±96,9 in II and III groups and noted 20 and 25,8 times increase compared to the control group ($p<0,001$). When performing assessment between groups, FK differed significantly from I group in II group and from I and II groups in III group ($p_1<0,001$; $p_2<0,05$).

Transferrin was 0,317±0,110 in I group, 0,137±0,063 in II group and 0,063±0,005 in III group. So, accordingly, transferrin decreased 4; 9,4 and 20,3 times in the groups compared to the control group. During the comparison of all three groups, accurate results were obtained.

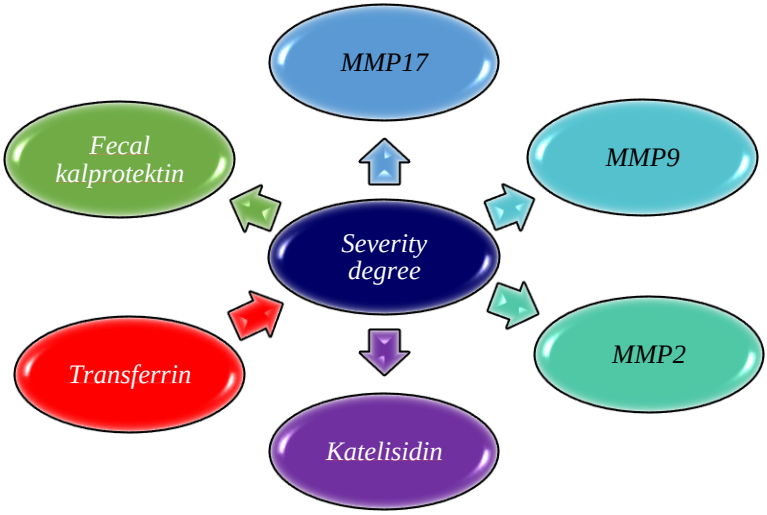
Lower level of transferrin was observed in III group that it also shows the more severe course of the disease (graphic 1).



Graphic 1. The level of biochemical markers in different groups during necrotizing enterocolitis in the newborns.

The next stage of research was conducted the correlation analysis between disease severity and markers in order to assess the clinical significance of biochemical markers during necrotizing enterocolitis. The results of the correlation analysis were assessed in terms of

quantitative using the Spearman's rank method (graphic 2).



Graphic 2. Correlation relationship between disease severity and biochemical markers.

The following correlation relationships were observed between the seriousness degree of necrotizing enterocolitis in newborns and the biochemical markers included in the research:

- moderately flat with MMP-9 (ρ_s=0,578, p<0,001), cathelicidin (ρ_s=0,525, p=0,001) and fecal calprotectin (ρ_s=0,766, p<0,001);
- weakly flat with MMP-17 (ρ_s=0,337, p=0,033), MMP-2 (ρ_s=0,401, p=0,010), weakly inverse correlation relationship with transferrin (ρ_s=0,347, p=0,028).

The described correlation relationships allow us to assess the clinical significance of markers according to the disease severity.

In order to determine the diagnostic significance of biochemical markers in patients with necrotizing enterocolitis in our research, the markers included in the examination were inspected and compared for the groups before and after treatment.

The comparison of biochemical markers for the groups in patients with necrotizing enterocolitis was showed in Table 1.

Table 1

The comparison of biochemical markers for the groups before and after treatment during necrotizing enterocolitis

Marker	I group (n=16)		II group (n=16)		III group (n=8)		P_{KU}	P_F
	BT	AT	BT	AT	BT	AT		
MMP-2, nq/ml	309,4 ±15,4 (249-519) * **	297,9 ±17,6 (221-473) * **	374,1 ±23,4 (270-598) ***#	335,1 ±24,2 (231-563) ***	480,8 ±87,8 (285-950) ***#	438,6 ±86,7 (219-882) ***#	0,040	0,015
MMP-9, nq/ml	367 ±20,5 (233-502) ***	318,4 ±16,6 (199-422) ***	412,3 ±19,7 (284-522) ***	378,6 ±20,8 (241-501) ***#	544,1 ±25,4 (484-671) ***###^^	501,6 ±40,5 (249-610) ***###^^	0,001	<0,001
MMP-17, nq/ml	983,6 ±75,7 (521-1444) ***	918,4 ±71,8 (463-1439) ***	1016,1 ±74,3 (533-1497) ***	927,4 ±67,1 (501-1399) ***	1426,6 ±142,5 (749-1989) ***##^^	1309,8 ±151,5 (702-1906) ***#^	0,035	0,007
KS, nq/ml	40,3 ±1,0 (33,5-47,8) ***	37,2 ±1,1 (28,8-45,1) ***	43,8 ±1,5 (37,1-55,4) ***	39,3 ±1,6 (31,1-53,6) ***	50,9 ±2,4 (41,3-61) *** #^^	48,9 ±2,3 (38,9-56,9) ***###^^	0,003	<0,001
TF, nmol/l	0,317 ±0,11 (0,04-1,08) ***	0,384 ±0,12 (0,04-1,33) ***	0,137 ±0,063 (0,04-1,07) ***	0,170 ±0,071 (0,05-1,22) ***	0,063 ±0,005 (0,04-0,09) ***	0,087 ±0,007 (0,07-0,12) ***	0,093	0,138
FK, mkq/mol	362,7 ±20 (242-480) ***	284,8 ±18,4 (159-421) ***	580,5 ±25,0 (421-719) ***###	452,1 ±27,9 (300-682) ***###	746,9 ±96,9 (331-1307) ***###^	587 ±68,9 (301-982) ***###^	0,001	<0,001

Note:

1. Brackets indicate M±m (95% CI)
2. Statistically sign. results for the Manny-Whitney non-parametric criterion::
- with the control group* – $p<0,05$; ** – $p<0,01$; *** – $p<0,001$
– with I group# – $p_1<0,05$; ## – $p_1<0,01$; ### – $p_1<0,001$
– with II group^ – $p_2<0,05$; ^^ – $p_2<0,01$; ^^^ – $p_2<0,001$
3. p (KU)- Results of variational examination according to Kruskal-Wallis criterion (comparison of three groups)
4. P_F- Results of one-factor dispersion examination according to Fisher criterion (comparison of three groups)

It was determined at the time of conduction of the comparative assessment between the groups that MMP-2 increased 6,9 times in I group, 8,3 times in II group and 10,7 times in III group compared to the control group (accordingly 309,4±15,4; 374,1±23,4; 480,8±87,8). When MMP-2 compared with other groups in III group, accurate results were obtained with I and II groups. Similarly, MMP-9 increased 3 times in I group, 3,4 times in II group and 4,5 times in III group and was 544,1±25,4. MMP-9 differed significantly from the control group in I and II groups, as well as in III group, an accurate result was obtained with I and II groups. Thus, MMP-9 was 544±25,4 in III group.

As can be seen from Table 1, different results were obtained after treatment in different groups of biochemical markers. Significant changes in MMP-2 levels were found in all three groups after treatment. So, although the level of MMP-2 was 309,4±15,4 in I group; 374,1±23,4 in II group; 480,8±87,8 in III group before treatment, this indicator decreased in all three groups after treatment, it formed 297,9±17,6; 335,1±24,2; 438,6±86,7 accordingly.

MMP-9 was 367±20,5 before treatment and 318,4±16,6 after treatment in I group; 412,3±19,7 before treatment and 378,6±20,8 after treatment in II group; 544,1±25,4 before treatment and 501,6±40,5 after treatment in III group and significantly differed from the control group and other groups.

The level of MMP-17, as in other MMPs, decreased in all groups after treatment. Thus, MMP-17 was 918±71.8 in I group, 927±67,1 in II group and 1309,8±151,5 in III group after treatment (before treatment, accordingly 983,6±75,7; 1016±74,3; 1426,6±142,5).

Although the level of cathelicidin was determined 40,3±1,0 in I group, 43,8±1,5 in II group before treatment, it decreased approximately the same after treatment in both groups and significantly differed from the control group ($p<0,001$)- 37,2±1,1 and 39,3±1,6. Cathelicidin (CATH) was 50,9±2,4 before treatment and 48,9±2,3 after treatment in III group and significantly differed from the control group and I and II groups.

The level of transferrin in the blood decreased in all three groups before treatment, slightly increased after treatment and approached to

the control group. Thus, TF (transferrin) was 0,384±0,12 in I group, 0,170±0,071 in II group and 0,087±0,007 in III group after treatment and significantly differed from the control group before and after treatment ($p<0,001$).

Fecal calprotectin in feces were identified in patients before and after treatment and a comparative assessment was performed. So, in case that fecal calprotectin (FC) was 362,7±20 in I group, 580,5±25 in II group and 746,9±96,9 in III group before treatment, decreased after treatment and for the groups, was 284,8±18,4, 452,1±27,9 and 587±68,9 accordingly ($p<0,001$, $p_1<0,001$, $p_2<0,05$).

In order to study the prognostic importance of biochemical markers during NEC in newborns and to assess the interaction between markers, the next stage of research were performed ROC analysis for these indicators.

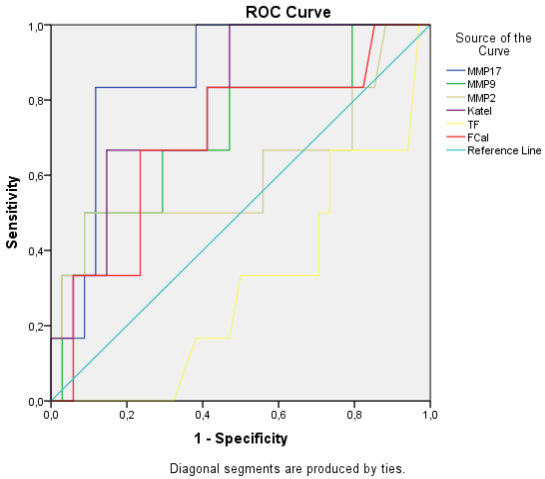
40 newborns identifying biochemical markers in our research were divided into 2 groups: the dead and the living. By dividing the variation interval of each indicator into small intervals, the specificity and sensitivity at each point were assessed and the ROC-curve (receiver operating characteristic) was constructed. The ideal curve is in the shape of "Γ". The farther the ROC curve is from the diagonal, the closer it is to this shape, the higher the specificity and sensitivity of the indicator. The area of the ROC-curve, the standard error, the asymptotic value, and the asymptotic upper and lower limit reliability interval of 95% were determined.

According to the ROC analysis, the area of MMP-17 marker was S=0,863±0,66 (95%CI: 0,734-0,992; p<0,005), MMP- 9 – S=0,716±1,22 (95%CI: 0,477-0,954; p=0,096), MMP-2– S=0,610±0,153 (95%CI: 0,310-0,911; p=0,0394), cathelicidin – S=0,794±0,086 (95%CI: 0,625-0,963; p=0,023), transferrin – S=0,301±0,106 (95%CI: 0,094-0,509; p=0,125), fecal calprotectin – S=0,694±0,120 (95%CI: 0,459-0,929; p=0,135) (graphic 3).

Apparently, among the studied indicators, MMP-17, cathelicidin and MMP-9 were selected with higher sensitivity and specificity. Other indicators also have statistically accurate diagnostic significance.

Then, «cut of point» was determined for each marker. The opti-

mal "intersection point" for MMP-17 is considered 1350 ng/ml. At this point, the sensitivity (Se) is equal to 83,3±15,2%, and the specificity (Sp) is equal to 88,2±5,5%. This “point” was ≥ 510 ng/ml – Se = 50,0±20,4%, Sp = 91,2±4,9% for MMP-9, ≥ 470 ng/ml Se = 50,0±20,4%, Sp = 91,2±4,9% for MMP-2; ≥41,2 ng/ml Se = 100,0±0,0%, Sp = 52,9±8,6% for cathelicidin; ≤ 0,065 – Se =66,7,4±19,3% , Sp = 70,6±7,8% for transferrin and ≥ 625– Se =66,7 ±19,2 %, Sp = 76,5±7,3% for fecal calprotectin. The total diagnostic weight test was 87,5% for MMP-17, 85% for MMP-9, and -85% for MMP-2, which indicates that the prognostic value of these markers is high.



Indicators	Area	Standard error	Asymptotic value	Asymptotic 95% CI:	
				Lower limit	Upper limit
MMP-17	0,863	0,066	0,005	0,734	0,992
MMP-9	0,716	0,122	0,096	0,477	0,954
MMP-2	0,610	0,153	0,394	0,310	0,911
Cathelicidin	0,794	0,086	0,023	0,625	0,963
Transferrin	0,301	0,106	0,125	0,094	0,509
Fecal calprotectin	0,694	0,120	0,135	0,459	0,929

Graphic 3. Statistical results of ROC-analysis characterizing the biochemical markers during necrotizing enterocolitis in newborns

The next stage was assessed the impact on the results of each factor through ANOVA (FS- Fisher-Snedecor) dispersion analysis. Higher indicator for the impact strength on the course of the disease was recorded in MMP-17- factor impact strength (EIF)=59,9 (95% CI: 64,2–55,5; p<0,001). And in other MMPs, indicators were as follows: MMP-9- EIF=20,4 (95% CI: 29,0–11,8; p<0,001), MMP-2- EIF=20,4 (95% CI: 29,0–11,8; p<0,001). MMP concentration change indicates the manifestation of septic process, complication of necrotic damages in the intestine and so, higher probability of non-satisfactory result.

The impact strength of other markers was as follows: CATH- EIF=13,3 (95% CI: 22,1–4,4; p<0,009), TF – EIF=8,4 (95% CI: 18,3–0; p <0,038), FK- EIF=12,7 (95% CI: 22,1–3,3; p <0,012).

In order to assess the relationships between indicators, the correlation analysis was performed in the next stage of research. The results of the correlation analysis were assessed in terms of quantitative using the Spearman's rank method.

In order to assess relationships between biochemical markers studied in our research and other indicators, the correlation analysis was performed. The results of the correlation analysis were assessed in terms of quantitative using the Spearman's rank method. At this time, the following numerous correlation relationships were determined:

- Moderately correlation relationship - inverse correlation relationship between cathelicidin and cerebral hemorrhage (ρ_s=0,659, p=0,006), cathelicidin and functional oval hole (ρ_s=0,658, p=0,006), and straight correlation relationship between fecal calprotectin and glucose (ρ_s=0,758, p=0,008) and between squamous epithelial in the feces (ρ_s=0,684, p=0,003)
- Weakly correlation relationship - inverse correlation relationship between MMP-17 and HE (ρ_s=0,501, p=0,048), MMP-17 and ESR (ρ_s=0,949, p=0,014), MMP-17 and functional oval hole (ρ_s=0,532, p=0,034), and straight correlation relationship between MMP-17 and MCHC (ρ_s=0,841, p=0,036), MMP-9 and MCHC (ρ_s=0,899, p=0,015), MMP-9 and toxoplasmosis (ρ_s=0,690, p=0,040).

After treatment, a straight correlation relationship between MMP-17 and cathelicidin (ρ_s=0,530, p=0,035) and fecal transferrin and cathelicidin (ρ_s=0,517, p=0,040) was recorded among biochemical markers.

So, during necrotizing enterocolitis, significant changes in the level of biochemical markers are found in accordance with the stages of the disease, which confirms the role of these markers in the diagnosis of the disease, differential diagnosis and choice of treatment tactics. In this case, a significant increase in the level of fecal calprotectin, a marker of inflammation of the gastrointestinal system is observed up to on average 14,7 times (p<0,001) compared with the control group. The identified changes show that the excretion of fecal calprotectin (FC) has a local character and determines the degree of involvement of the intestine in the inflammatory process and the activity of the inflammatory process in the intestinal wall. This suggests the use of FC as a non-invasive marker in the diagnosis of necrotizing enterocolitis. Changes in the concentration of other biochemical markers have a straight correlation relationship and increase according to the stages of the disease.

According to our research, it was determined that changes in the concentration of biochemical markers are considered predictors of the initial period of NEC and vary depending on the severity of the disease and its continuation duration. Changes in the level of these markers in patients against the background of complex treatment indicate an unsatisfactory course of the disease and its progression to stage III.

The examination of the described markers provides a basis for their use in neonatal practice for the diagnosis and course prognosis of NEC.

CONCLUSIONS

1. Newborns (60,0±4,7%) who were born from mothers with vomiting (84,5±3,4%), anemia (63,6±4,6%), intrauterine infections (20,9±3,9%) during pregnancy and artificially fed from the first days are at risk for the development of necrotizing enterocolitis [1, 2, 6,

10, 19].

2. During necrotizing enterocolitis in newborns, a significant increase in the level of fecal calprotectin, a marker of inflammation of the gastrointestinal system, is observed up to on average 14,7 times ($p<0,001$) compared with the control group. This suggests using this indicator as a non-invasive marker in the diagnosis of necrotizing enterocolitis [3, 5, 12].

3. For the purpose of prognostic assessment during necrotizing enterocolitis in newborns, the total diagnostic weight test was 87,5% for MMP-17, 85,0% for MMP-9 and -85,0% for MMP-2 in the examination of matrix metalloproteinases, a molecular biochemical marker, which indicates that the prognostic value of these markers is high. It differs from biochemical parameters in regard to high sensitivity (66,7±19,2%) and specificity (70,6 ± 7,8%) of transferrin. During necrotizing enterocolitis, higher indicator for the impact strength on the course of the disease was recorded in MMP-17- EIF =59,9 (95% CI: 64,2–55,5; $p<0,001$) [9, 16, 17, 20, 21, 22, 23, 24].

4. Among the biochemical markers studied in necrotic enterocolitis, MMP-17, cathelicidin and MMP-9 differed in regard to their higher sensitivity and specificity. Thus, according to the ROC analysis, the area of the ROC curve for MMP-17 marker is S = 0,863 ± 0,066 (95% CI: 0,734-0,992; p = 0.005), for the cathelicidin marker - S = 0,794±0,086 (95% CI: 0,625-0,963; p=0,023), for MMP-9 marker - S = 0,716±0,122 (95% CI: 0,477-0,954; p = 0,096) [13, 14].

5. Biochemical markers included in the research with the severity degree of necrotizing enterocolitis in newborns were mainly observed during exact correlation relationship between MMP-9 (ρ_s=0,578, p=0,001), cathelicidin (ρ_s=0,525, p=0,001), fecal calprotectin (ρ_s=0,766, p=0,001). This allows us to assess the clinical significance of markers according to the severity of the disease [4, 7, 11, 18].

PRACTICAL RECOMMENDATIONS

1. It is recommended to conduct complex examinations and to appoint fecal calprotectin, a non-invasive marker for early diagnosis

of necrotizing enterocolitis in newborns and assessment of the severity of the inflammatory process in the intestine.

2. Appointment of matrix metalloproteinases (MMP-2, MMP-9, MMP-17) and cathelicidin, which are molecular biochemical markers in the early diagnosis of the disease during necrotizing enterocolitis in newborns, is of practical importance in assessing the clinical course of the disease and determining complications.

3. It is recommended to take adequate treatment measures for patients during necrotizing enterocolitis and to appoint MMP-17, a biochemical marker in order to determine the prognosis of the disease.

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List of abbreviations

ANOVA – analysis of variance
ARVI – acute respiratory viral infection
AVL – artificial ventilation of the lungs
CATH – cathelicidin
CI – confidence interval
EIF – efficiency influence of factor
ERS – erythrocyte sedimentation rate
FC – fecal calprotectin
GIT – gastrointestinal tract
HCT – hematocrit
HGB – hemoglobin
IEA – immunoenzyme analysis
MCH – mean corpuscular hemoglobin
MCHC – mean corpuscular hemoglobin concentration
MCV – mean corpuscular volume
MMP – matrix metalloproteinase
NEC – necrotizing enterocolitis
PLT – platelets
RBC – red blood cells
RDW CV – red cell distribution width, coefficient of variation
RDW SD – red cell distribution width, standard deviation
TF – transferrin
USS – ultrasound scan
WBC – white blood cells

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